REMARKS

Applicants thank the Examiner for his review of the instant application. For the reasons stated below, the rejections of the presently pending claims are respectfully traversed. Claims 6-8, and 11-17 are presented for examination.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of the pending claims under 35 U.S.C. § 101 as lacking a specific and substantial asserted utility or a well established utility. The PTO states that the specification fails to disclose enough information about the invention to make its usefulness immediately apparent. The PTO also states that Applicants' evidence that differential expression of PRO1753 mRNA in tumor tissue relative to normal tissue is insufficient evidence that the claimed PRO1753 polypeptide will function as a cancer diagnostic.

For the reasons set forth below, Applicants respectfully disagree.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true.

As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. Even if the correlation between Applicants evidence and the asserted utility is not exact, such that there are exceptions to the correlation between the evidence and the asserted utility, this is sufficient to establish a utility. *See Fujikawa v. Wattanasin,* 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (stating that "a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices," and thus a utility was established even though there were exceptions to the correlation between the disclosed *in vitro* data and asserted *in vivo* utility). Therefore, exceptions

between the evidence disclosed and the asserted utility is permissible – **the standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

1. Applicants have provided reliable evidence that mRNA for the PRO1753 polypeptide is expressed at least two-fold higher in esophageal tumor tissue as compared to normal esophageal tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* an increase, generally leads to a corresponding change in the level of the encoded protein, *e.g.* an increase;

3. Given the differential expression of the PRO1753 mRNA in esophageal tumors as compared to normal esophageal tissue, it is more likely than not that the PRO1753 polypeptide is also differentially expressed in esophageal tumors as compared to normal esophageal tissue, making the claimed polypeptides useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making two arguments in response to Applicants' asserted utility:

1. The PTO challenges the reliability of the evidence reported in Example 18, stating that "the skilled artisan would not know if the reported change in PRO1753 transcripts is tumor-dependent or tumor-independent." *Office Action* at 7;

2. The PTO argues that "[t]he skilled artisan would not know if or how expression of the PRO1753 polypeptide would change in tumors because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis." *Office Action* at 5; citing Haynes *et al.*; Molecular Biology of the Cell, 3rd ed.; Molecular Biology of the Cell, 4th ed.; Genes VI; Polakis Declaration; and Meric.

Applicants respectfully submit that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

The PTO has Concluded that the data in Example 18 are Sufficient to Establish the Utility of the Claimed Invention

As an initial matter, Applicants point out that in other applications filed by Applicants that rely on *data from the exact same disclosure, Example 18*, and in which the Applicants have submitted *substantially the same references* in support of their asserted utility, the PTO has concluded that:

> Based on the totality of evidence of record, **one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels,** absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding PRO1180, also supports a conclusion of differential expression of PRO1180 polypeptide. Therefore, one of ordinary skill in the art would be able to use the PRO1180 polypeptide diagnostically for distinguishing normal kidney and rectal tumor tissues compared to kidney tumor and normal rectal tissue, as asserted by Applicant. *Examiner's Reasons for Allowance, Application No. 10/063,529* (emphasis added).

See also *Examiners Reasons for Allowance* in Application No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583, all of which conclude that the data presented in Example 18, which demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides, also support a conclusion of differential expression of the PRO polypeptides, making the claimed PRO polypeptides and antibodies that bind the PRO polypeptides useful for diagnostic purposes.

Applicants therefore request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and the numerous cited references, as was done in the other applications referenced above.

Applicants have established that the Gene Encoding the PRO1753 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO1753 gene is differentially expressed in esophageal tumor tissue as compared to normal esophageal tissue, and is therefore useful as a diagnostic tool for esophageal cancer. This assertion is based on the results of RT-PCR analysis

of pooled normal esophageal tissue and pooled esophageal tumor tissue using methods that are well-established in the art.

This utility is substantial, *i.e.* distinguishing tumor cells from normal cells is not an insubstantial or trivial utility without a real world use, and it is specific, *i.e.* it is directed to specific disease and is not a utility that the entire class of nucleic acids shares. Finally, this asserted utility is credible, as one of skill in the art would readily believe that a nucleic acid sequence can be used as a marker to distinguish tumor tissue from normal tissue.

Applicants remind the Examiner that Applicants enjoy a presumption that their assertions are true. The Examiner must approach Applicants' assertion of utility as being sufficient to satisfy the utility requirement. M.P.E.P. §2107.02, "Procedural Considerations Related to Rejections for Lack of Utility," states:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. *M.P.E.P. §2107.02* at III. A., *quoting In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (C.C.P.A. 1974) (emphasis in original).
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> Thus, *Langer* and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. ... Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. ... Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons. *Id.*

With respect to the use of the PRO1753 nucleic acid to distinguish tumor from normal tissue, the Examiner must accept this assertion as true "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility." Therefore, the question is whether the PTO has established that there is a reason to doubt the objective truth of Applicants' assertion that using standard RT-PCR procedures to examine the expression of the PRO1753 mRNA in pooled normal esophageal samples and pooled esophageal tumor samples, Applicants

discovered that PRO1753 mRNA is differentially expressed between normal and tumor such that it can be used as a diagnostic tool.

In response to Applicants' asserted utility, the PTO asserts that "the skilled artisan would not know if the reported change in PRO1753 transcripts is tumor-dependent or tumor-independent." *Office Action* at 7. This assertion is based on three sentences from a letter to the editor by LaBaer about the Hu reference, and a related statement in the Hu *et al.* reference, of which LaBaer was the primary investigator:

> In the accelerating quest for disease biomarkers, the use of high-throughput technologies, such as DNA microarrays and proteomics experiments, has produced vast datasets identifying thousands of genes whose expression patterns differ in diseased versus normal samples. Although many of these differences may reach statistical significance, they are not always biologically meaningful. For example, reports of mRNA or protein changes of as little as two-fold are not uncommon, and although some changes of this magnitude turn out to be important, most are attributable to disease-independent differences between the samples. *LaBaer* at 976.

> It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful. *Hu* at 411, right column, first full paragraph.

Thus, the PTO is arguing that because "high throughput technologies, such as DNA microarrays" produce differences in mRNA that are attributable to "disease-independent differences between samples," this establishes "a reason for one skilled in the art to question the objective truth" of Applicants' asserted utility which is based on RT-PCR analysis of pooled samples of normal and tumor tissue, not microarrays.

Applicants respectfully submit that one of skill in the art would not accept that the PTO has established a basis to doubt Applicants' asserted utility. As Applicants' have previously stated, those of skill in the art recognize that RT-PCR is a more accurate and reliable technique than microarrays (see, e.g., Kuo *et al.*, (Proteomics 2005; 5(4):894-906), previously submitted). Therefore, it would be readily apparent to one skilled in the art that opinions regarding data from high-throughput techniques such as microarrays are simply not relevant to Applicants' RT-PCR data, and are not a reason to doubt the truth of Applicants' asserted utility. Thus, even if accurate, a point which Applicants do not concede, Hu's and LaBaer's opinions regarding

microarray studies are not relevant to the utility of the instant application which does not rely on microarray data.

Applicants emphasize that they are not asserting that microarray data are not reliable (that is apparently the PTO's position based on Hu and LaBaer), merely that Applicants are using a method that is recognized by those of skill in the art as more reliable and sensitive.

In response to Applicants' previous arguments based on Kuo, the PTO states that Kuo is not persuasive because "it cannot be ascertained if Kuo's microarray data was [*sic*] consistent or inconsistent with Kuo's RT-PCR data. Kuo's poor correlation between microarray and proteomic expression profiles does not speak to changes in mRNA attributable to disease-independent differences between samples and does not speak to the accuracy and reliability of RT-PCR." *Office Action* at 2.

The PTO's argument misses the point of Applicants' reliance on Kuo. Kuo is cited as evidence to support Applicants' assertion that Applicants' PCR data are more accurate and reliable than the microarray technique commented on by Hu and LaBaer. Kuo supports this assertion because it is evidence that one of skill in the art would regard PCR as a more accurate and reliable method of assessing changes in mRNA. Thus, whether or not the microarray technique commented on by Hu and LaBaer yields "disease-independent" results is not relevant to Applicants' data because, as evidenced by Kuo, PCR data such as Applicants' are more accurate and reliable than the microarray data relied on by Hu and LaBaer. Until the PTO provides evidence that transcript changes detected by PCR analysis of pooled normal and tumor samples are often "disease-independent," the PTO's rejection of the data in Example 18 based on Hu and LaBaer is misplaced, and Applicants' asserted utility must be presumed true.

Applicants also note that neither Hu nor LaBaer cite any references to support their assertions that "most [microarray differences] are attributable to disease-independent differences between the samples" and that "it is not always clear if [the microarray differences] are biologically meaningful." In the absence of any supporting references, Applicants cannot independently evaluate these statements to determine what is meant by "disease-independent differences" and "biologically meaningful." Read in light of the entire article and accompanying letter to the editor, Applicants assert that these statements should be interpreted to mean that the observed differences do not play a role in the development or progression of the disease state, or

that such a role in the disease state has not yet been published. As Applicants have previously stated, a differentially expressed mRNA can serve as a marker of a disease even if it is "disease-independent" in the sense that it has no role in the cause or progression of a disease, or if any such role is not yet published in the literature. Applicants invite the PTO to provide support for an alternate interpretation of "disease-independent" as used in Hu and LaBaer.

With respect to Applicants' arguments that Hu and LaBaer are silent regarding the reliability of pooled samples, which are incorporated herein by reference, the PTO states:

> [T]he asserted diagnostic utility of the PRO1753 polypeptide depends upon its ability to differentiate normal tissue from tumor tissue. In practicing the invention some value for PRO1753 polypeptide expression must be obtained in order to make this distinction. Establishing a cutoff value for this distinction would be difficult unless one knows the typical degree of variation within the pool, which applicants have not provided. There is no evidence of record concerning the normal range in PRO1753 mRNA levels or PRO1753 polypeptide levels in normal tissue or tumor tissue. There is no evidence of record that a normal range of PRO1753 mRNA or PRO1753 polypeptide levels could be defined that would distinguish normal tissue from tumor tissue. Without knowledge of the typical degree of variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue. Pooled samples would also obscure the variation between samples, making the disclosed results for PRO1753 polynucleotide expression less useful, accurate and informative than if results from individual samples had been provided. In fact, the range of values from normal and/or tumor tissue could be so broad that it would be impossible to distinguish normal tissue from tumor tissue. *Office Action* at 4-5.

The PTO presents no evidence to support these assertions. Thus, the PTO uses conclusory and unsupported arguments as the basis for dismissing the declaration of an expert. As such, the PTO's position is inconsistent with the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered" (*66 Fed. Reg. 1098, Part IIB (2001)*) and also is inconsistent with the requirement of the PTO to support its assertions of fact. *See In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001). Absent supporting evidence, it is inappropriate for the PTO to dismiss Applicants' arguments and Mr. Grimaldi's opinion regarding pooled samples simply because the PTO wishes to take a contrarian position on the use of pooled samples in diagnostics.

Regarding the substance of the above-quoted text from the PTO regarding pooled samples, Applicants traverse this position and maintain that their expert has established that "[d]ata from pooled samples is more likely to be accurate than data obtained from a sample from a single individual." *First Grimaldi Declaration* at ¶5. As to the PTO's statement that "[i]n fact, the range of values from normal and/or tumor tissue could be so broad that it would be impossible to distinguish normal tissue from tumor tissue," (*Office Action* at 5, emphasis added), Applicants note that the Grimaldi declaration make clear that, in fact, "the results of the gene expression studies indicate that the genes of interest can be used to differentiate tumor from normal." *First Grimaldi Declaration* at ¶7. Applicants refrain from further rebutting the PTO's assertions because there presently are no facts on the record to support a position other than that of Mr. Grimaldi's. Applicants respectfully request that the PTO provide evidentiary support for its assertions regarding pooled samples in order to fully develop these issues under examination.

As for the PTO's statement that the first Grimaldi declaration is "in contrast with the specification's teachings," (see *Office Action* at 4), Applicants do not know how to respond since the Office has not explained how the declaration is in contrast with the quoted portion of the specification or what relevance any contrast between the two statements has to Applicants' asserted utility. Similarly, the Office's statement that "Hu is evidence that a skilled artisan would consider the precise level of PRO1753 gene expression as relevant" is not supported by any reasoning or citation to Hu. Applicants' are unaware of any teaching in Hu regarding the need for a "precise level of PRO1753 gene expression" to use it as a molecular marker to distinguish tumor tissue from normal tissue. In fact, Hu and LaBaer teach nothing at all regarding developing diagnostic markers of cancer.

In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1753 mRNA between esophageal tumor tissue as compared to normal esophageal tissue. Applicants' assertion that PRO1753 mRNA can be used to distinguish esophageal tumor tissue from normal esophageal tissue must be presumed true by the Examiner unless there is a reason that one of skill in the art would doubt the objective truth of Applicants' statements. Applicants have shown that the references by Hu and LaBaer are inapplicable to Applicants' RT-PCR data, and the PTO

has provided no evidentiary basis for dismissing the Grimaldi Declaration. Thus, any challenge to the sufficiency of the data with respect to the utility of the nucleic acid is inappropriate.

Therefore, the only issue which remains is whether the data in Example 18 regarding differential expression of the PRO1753 mRNA are reasonably correlated with differential expression of the PRO1753 polypeptide such that the claimed polypeptides have utility as diagnostic tools as well. As discussed below, even if the PTO has established a reasonable doubt regarding Applicants' assertion that they are reasonably correlated, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level lead to corresponding changes in protein level.

The PTO's Evidence is Not Relevant to Determining Whether a Change in mRNA Level for a Particular Gene leads to a Corresponding Change in the Level of the Encoded Protein

Applicants turn next to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1753 polypeptide in esophageal tumors, it is likely that the PRO1753 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools. As stated above, the Examiner should approach these assertions of utility with a presumption that they are true.

In response to Applicants' assertion, the PTO cites, among others, Haynes *et al.* (Electrophoresis, 1998; 19(11):1862-71), as well as several references relied on by Applicants, Molecular Biology of the Cell, 3rd ed.; Molecular Biology of the Cell, 4th ed.; Genes VI; Polakis Declaration; and Meric, for support of its argument that "the skilled artisan would not know if or how expression of the PRO1753 polypeptide would change in tumors." *Office Action* at 5.

Applicants have previously discussed at length why the Haynes reference is not relevant to the issue of whether differential mRNA expression levels for a particular gene lead to corresponding differential expression of the encoded protein. Applicants incorporate by reference the previous arguments, and will not repeat them here. However, in an attempt to

illustrate why references which relate to static global levels of mRNA and protein across different genes are not relevant to Applicants' asserted utility, Applicants provide the following.

Haynes, and similar references, looked for a correlation between the level of mRNA and corresponding protein by plotting a single measurement of mRNA level vs. protein level for a large group of different genes. The only way that such a plot would result in a significant correlation is if there exists a global ratio between mRNA levels and protein levels common across all genes, i.e., that for every X copies of an mRNA, there are Y copies of the encoded protein, such that the ratio of X:Y is constant across all genes. If such a global ratio existed, then plotting mRNA levels for different genes against their corresponding protein levels would result in a strong correlation. For example, if the global ratio is 2:1, then 100 transcripts of gene X would result in about 50 copies of protein X, 500 transcripts of gene Y would result in about 250 copies of protein Y, and 1000 transcripts of gene Z would result in about 500 copies of protein Z. Plotting the amount of mRNA against the amount of protein for these different genes in a sample would result in a strong correlation.

This is what Haynes and similar references examined. According to the PTO, they did not find a strong correlation. This is because the ratio between transcript copy number and protein level is apparently not the same for all genes. As a result of these findings, Haynes concluded that protein levels cannot be accurately calculated from mRNA levels, and that "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification." *Haynes* at 1863, right column, full paragraph 2. Regardless of whether this conclusion is correct or not, it is not contrary to Applicants' assertion, and is not relevant to the question of whether differential mRNA levels for a particular gene lead to corresponding differential expression of the encoded protein.

In contrast, Applicants' asserted utility does not require knowledge of, or even the existence of, a global ratio between mRNA levels and protein levels. Nor do Applicants' assertions require calculation of protein levels based on measured mRNA levels. Unlike Haynes, Applicants are not relying on a single measure of mRNA for a particular gene and then attempting to calculate protein levels based on a global ratio between mRNA and protein levels. Instead, Applicants are relying on differential mRNA expression, where mRNA levels are

measured in two different conditions, i.e. tumor and normal. Applicants assert that a difference in mRNA expression level for a particular gene typically leads to a corresponding difference in the expression level of the encoded protein. *See, e.g., First Grimaldi Declaration* at paragraph 7. The Haynes reference, and similar studies, are applicable only to a completely unrelated issue – whether a single measure of mRNA levels can be used to predict protein levels – and therefore, none of the data or conclusions of these references have any bearing on Applicants' assertions.

> The PTO repeatedly relies on the assertion that:
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> The skilled artisan would not know if or how expression of the PRO1753 polypeptide would change in tumors because there are numerous levels of control of protein synthesis, degradation, processing, and modification, that are only apparent by direct protein analysis. *Office Action* at 5; *see also Office Action* at 9-10.

This assertion is based on a statement in Haynes. However, as discussed above, the authors of Haynes based their conclusions on a lack of a global relationship between mRNA levels and protein levels across different genes. This is not relevant to the question of whether one of skill in the art would expect changes in mRNA level to lead to changes in protein level. The authors of Haynes did not address this question, and their statements regarding the ability to calculate protein levels based on mRNA levels refer only to their experiments looking for a global correlation.

In addition to Haynes, the PTO relies on Molecular Biology of the Cell, 3rd ed., Molecular Biology of the Cell, 4th ed., Genes VI, the Polakis Declaration, and Meric (*see Office Action* at 6). Applicants note that the PTO is not considering the entire teachings of these references when it chooses to ignore portions of the text which support Applicants. For example, the PTO cites Genes VI as teaching that "production of RNA cannot inevitably be equated with production of protein," (*see Office Action* at 6), while the full statement reads "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added). How each of these references support Applicants' position when read in their entirety is of record, and will not be repeated here.

However, even if one acknowledges that there are numerous levels of control of protein synthesis, degradation, processing and modification, this is still not contrary to Applicants' assertion that when mRNA levels for a particular gene are changed, there is generally a corresponding change in protein levels. Just because a cell has numerous means of modulating protein levels, this does not prohibit the possibility that a change in mRNA level generally results in change in protein level – these are not mutually exclusive propositions. Therefore, one must look at actual experiments where a change in mRNA level was assessed to determine if the change generally results in a corresponding change in protein levels. None of the references cited by the PTO teach to the contrary, and Applicants' evidence discussed below teaches that this is in fact the case.

In conclusion, Applicants have shown that the references such as Haynes that examine mRNA/protein relationships across different genes are simply not relevant to the issue of whether a change in mRNA levels leads to a corresponding change in the level of the encoded protein. Similarly, the other references relied on by the PTO support Applicants' position when read in their entirety. Taken together, the PTO's arguments are not sufficient to satisfy the burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Applicants' Evidence Establishes that a Change in mRNA Level for a Particular Gene leads to Corresponding Change in the Level of the Encoded Protein

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, a copy of a declaration of Paul Polakis, Ph.D., excerpts from the Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002). In addition, in the most recent response, Applicants submitted over 100 additional references in support of their assertion that changes in mRNA for a particular gene are positively correlated to changes in the corresponding protein level, and a second declaration by Dr. Polakis. The details of the teachings

of these declarations and references, and how they support Applicants' asserted utility, are of record and will not be repeated here.

Applicants submit herewith a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 1). Dr. Scott is an independent expert in the field of molecular diagnostics, with over 15 years experience. He is the author of over 40 scientific publications in the fields of protein biology, gene discovery, and cancer, and is an inventor on several issued patents. His curriculum vitae is attached to the declaration. In paragraph 10 of his declaration, Dr. Scott states:

> One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels. *Scott Declaration* at ¶10 (emphasis added).

Applicants submit the opinion of yet another expert in the field that changes in mRNA level for a particular protein in a given tissue generally lead to a corresponding change in the level of the encoded protein. Importantly, Dr. Scott also states that, contrary to the contentions of the PTO, diagnostic markers can be identified "without the need to directly measure individual protein expression levels." This opinion is supported by Dr. Scott's extensive experience in the field, as well as the fact that an entire industry has developed around technology to assess differential mRNA expression. As stated previously, there would be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels.

The case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. *See in re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976); *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996), *quoting In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). Furthermore, the

Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." *66 Fed. Reg. 1098, Part IIB (2001).*

In summary, Applicants have submitted herewith additional expert Declarations in addition to the declarations and over 115 references already of record, which support Applicants' asserted utility, either directly or indirectly. This evidence supports the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions. However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1753 mRNA is differentially expressed in esophageal tumor tissue as compared to normal esophageal tissue, the PRO1753 polypeptide will likewise be differentially expressed. This differential expression of the PRO1753 polypeptide makes the claimed polypeptides useful as diagnostic tools for cancer, particularly esophageal cancer.

The PTO's Position is Inconsistent with the Utility Guidelines and the Courts

In response to Applicants' evidence and arguments, the PTO takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed

polypeptides – specifically, direct evidence of differential expression of PRO1753 polypeptide in tumor and normal tissue. Applicants submit that this requirement is inconsistent with the Utility Guidelines and the courts.

In response to the over 100 supporting references submitted in Applicants' previous response, the PTO makes the following conclusory argument:

> Applicants' additional supporting references (Exhibits 4-21, filed 05 /22/2006) have been considered. However, none of this evidence discloses anything specific regarding PRO1753 mRNA expression, PRO1753 polypeptide expression, or the correlation between the two in normal tissue and tumor tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1753 transcripts and PRO1753 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the first and second Polakis declarations. Regarding Orntoft and Futcher, there is no evidence of record that PRO1753 mRNA or protein is either abundantly expressed or abundantly under-expressed. Hu cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. *Office Action* at 12 (emphasis added).
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> The specification does not establish if the disclosed change in PRO1753 polypeptide expression is one of those cases where this [*sic*] is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Applicants have not provided any testing of PRO1753 polypeptide expression. ... In the absence of any testing of the expression of PRO1753 polypeptide, the specification does not provide some immediate benefit to the public for the PRO1753 polypeptide and the antibodies thereto. The correlation between the disclosed change in PRO1753 mRNA and a change in PRO1753 polypeptide expression is unknown and is not disclosed. *Office Action* at 12-13 (emphasis added).
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> Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO1753 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO1753 transcripts and PRO1753 polypeptide expression to argue that it is more likely than not that a change in PRO1753 transcripts is correlated with an assumed change in PRO1753 polypeptide expression. Without any evidence of the expression of PRO1753 in

> tumor tissue this argument is of no avail to Applicants. *Office Action* at 13 (emphasis added).

Thus, the PTO implies the following argument: (1) the evidence of record demonstrates that there are exceptions to the general rule that increased mRNA levels correspond to increased levels of the encoded polypeptide; (2) because such exceptions exist, it is mandatory that specific data of differential PRO1753 polypeptide expression in esophageal tumor tissue as compared to normal esophageal tissue be disclosed; and (3) since such is not disclosed, the claimed polypeptides have no substantial utility.

Adopting the PTO's standard for utility would result in a per se rule that a difference in mRNA expression cannot establish a utility for the encoded polypeptide and antibodies thereto. Thus, the PTO chooses to heighten the utility requirement to require specific, direct evidence of utility when there are exceptions to a generally accepted rule that is relied upon for utility. This heightened utility requirement is inconsistent with the Utility Guidelines and the courts. There is no requirement that utility be dispositively proven:

> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

Nor is there requirement that only direct evidence of utility is sufficient to establish utility. Instead, it is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856. Furthermore, there is no requirement that indirect evidence necessarily and always prove actual utility. Instead, there only need be a reasonable correlation between the indirect evidence and the asserted utility. *Id.* at 857, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051. The indirect evidence need not absolutely prove the asserted utility. All that is required is that the tests be reasonably indicative of the asserted utility. In other words, there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a reasonable probability, that the novel compound will possess the asserted utility. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564.

The PTO appears to consider the above guidance from the courts inapplicable to the present situation because in those cases the claimed compound had been tested, and, in the present case, the claimed polypeptides have not been tested. However, the PTO's position fails to recognize the issue in question for the above cases. The issue in question was whether or not Appellants' evidence (*in vitro* or animal testing of compound), which was different in nature from the asserted utility (therapeutic use of compound), was sufficient to fulfill the requirements of 35 U.S.C. §101 when there was a reasonable link between Appellants' evidence and the asserted utility. In the present case, Applicants submit that their evidence (differential mRNA expression) is reasonably linked to the asserted utility (diagnostic use of the encoded polypeptide). Insofar as it is uncontested that differential mRNA expression is reasonably linked to differential polypeptide expression, Applicants submit that such linkage is sufficient to fulfill the requirements of 35 U.S.C. §101 as provided by the guidance of the Utility Guidelines and the courts.

The PTO dismisses the above direction from the Utility Guidelines and the Courts stating:

> Applicants' utility standard would mandate only a showing that it is "not implausible" that the invention will work for its intended purpose. If mere plausibility were the test for how to use a claimed invention, Applicants could obtain patent rights to "inventions" based on a disclosure consisting of little more than guesses as to the likelihood of their success. *Office Action* at 7 (emphasis added).

Applicants emphasize that it is not "Applicants' utility standard" which is described above, but rather the utility standard established by the PTO's guidelines based on the law as stated by the Courts. The M.P.E.P., citing the relevant case law from the Courts, states that the standard for establishing utility is "more likely than not true":

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980)... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

Because the standard for satisfying the utility requirement is low – more likely than not true – the M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely** sustained by federal courts. Generally speaking, in these **rare** cases, the 35 U.S.C. 101 rejection was sustained [] because the applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. *M.P.E.P.* § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (C.C.P.A. 1967) (underline emphasis in original, bold emphasis added).

In conclusion, the PTO's heightened requirement for establishing utility of the presently claimed polypeptides is contrary to the Utility Guidelines and the courts: it is sufficient to present evidence of differential mRNA expression since it is understood in the art that differential mRNA expression is reasonably linked to differential polypeptide expression. As discussed above, even if the PTO has presented evidence that changes in mRNA expression are not always correlated with changes in protein expression, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level typically lead to corresponding changes in protein level. As such, Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO1753 mRNA is differentially expressed in esophageal tumor tissue as compared to normal esophageal tissue, the PRO1753 polypeptide will likewise be differentially expressed in esophageal tumors. As noted above, the PTO has reached the same conclusion in other applications filed by Applicants that rely on *data from the exact same disclosure, Example 18*, and in which Applicants have submitted *substantially the same references* in support of their asserted utility. Accordingly, when the evidence is applied to the proper standard for utility, it is clear that this differential expression of the PRO1753 polypeptide establishes the claimed polypeptides useful as diagnostic tools for cancer, particularly esophageal cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed polypeptides related to PRO1753. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1753 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene for the PRO1753 polypeptide is differentially expressed by at least two-fold in esophageal tumors as compared to normal esophageal tissue. These data are strong evidence that the PRO1753 gene and polypeptide are associated with esophageal tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1753 gene and polypeptide with a specific disease. The asserted utility for the claimed polypeptides as diagnostic tools for cancer, particularly esophageal tumors, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Utility – Conclusion

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (same); *Nelson v. Bowler*, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same). In addition, utility need only be shown to be "more likely than not true," not to a statistical certainty. *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. The PTO has reached this conclusion in other applications filed by Applicants that rely on data from the exact same disclosure, Example 18, and in which the Applicants have submitted substantially the same references in support of their asserted utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also maintains its rejection of pending Claims 6-8, and 11-17 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. *Office Action* at 14. In addition, the PTO asserts that the enablement would not be commensurate in scope with pending Claims 14-17. *Office Action* at 15-17.

The PTO has Failed to Establish a Reasonable Basis to Question the Enablement of the Pending Claims

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

With respect to Claims 14-17, which recite the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples," the PTO states that "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *Id.* at 15. In response to Applicants' previous arguments, the PTO states:

> All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. The specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO, as indicated below:
>
> > "Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either

> inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231.

> Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO: 110, and possessing any and/or all underlying biological activities. The level of experimentation required to make and use such an invention is clearly beyond the level of enablement provided by the specification because the specification provides no disclosure of any biological activity of the native or naturally-occurring PRO1753 polypeptide SEQ ID NO: 110. *Office Action* at 15-16 (emphasis added).

As noted previously, the PTO has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See M.P.E.P.* § 2164.04. A specification teaching how to make and use the claimed subject matter must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. *Id.* The above arguments fail to meet this burden because they are fundamentally flawed for at least two reasons.

First, the PTO is relying on a definition of the term "active" or "activity" found in the specification. However, the claims at issue do not use the terms "active" or "activity." Therefore, the PTO is impermissibly importing a limitation into the claims from the specification.

Second, even if the PTO were correct to suggest that the claimed polypeptides of claims 14-17 were required to be "active," nothing in the quoted portion of the specification suggests that the "specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO" as the PTO suggests. The PTO quotes the specification as stating "'biological' activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO **other than the ability to induce the production of an antibody** against an antigenic epitope possessed by a native or naturally-occurring PRO and an 'immunological' activity refers to the ability to induce the production of an antibody

against an antigenic epitope possessed by a native or naturally-occurring PRO." Thus, Applicants clearly contemplated that "biological" activity was distinct from "immunological" activity. In addition, according to the PTO, the specification teaches that "'Active' or 'activity' for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological **and/or** an immunological activity of native or naturally-occurring PRO." Clearly, Applicants contemplated that an "active" polypeptide can have "biological activity" **or** "immunological activity." Thus, the specification clearly teaches that a PRO polypeptide can retain "biological" activity, which does not include immunological activity, "immunological" activity, which does not include biological activity, **or** both.

Therefore, even if Applicants have failed to disclose the "biological" activity of the PRO polypeptide as the PTO asserts, this is not relevant to the enablement of the claims at issue because: (1) the claims do not recite the defined terms "active," "activity," "biological activity" or "immunological activity;" and (2) nothing in the specification requires immunologically active polypeptides to also be "biologically active."

The PTO also argues that:

> Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal samples is essential to Applicants' claimed genus of variant polypeptides. The specification defines antibody specificity as follows:
>
> > An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.
>
> The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. The level of ingenuity required to make such an invention is clearly beyond that to be expected of skilled artisans. The specification does not disclose how this would be accomplished. *Office Action* at 16.

Applicants maintain that Claims 14-17 do not require that the variant polypeptides of Claims 14-17 are capable of generating antibodies which bind the polypeptide of SEQ ID NO:110 without binding to the variant polypeptides themselves. Rather, the subject matter

within the scope of Claims 14-17 includes variant polypeptides which can be used to generate antibodies which bind to both the variant polypeptide used to generate them and to the polypeptide of SEQ ID NO:110, but which antibodies "can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples." Indeed, the PTO will appreciate that, in view of the high degree of homology between the polypeptides of Claims 14-17 and the polypeptide of SEQ ID NO:110, there are many antibodies which will bind to both polypeptides and, accordingly, the polypeptides of Claims 14-17 are useful for producing antibodies which can be used as diagnostic agents for detecting the polypeptide of SEQ ID NO:110 in a sample.

As all of the PTO's arguments attempting to establish a reasonable basis to question the enablement provided for the claimed invention are fundamentally flawed, the PTO has again failed to provide sufficient evidence to support a *prima facie* rejection of Claims 14-17. *See M.P.E.P.* § 2164.04.

A specification teaching how to make and use the claimed subject matter must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. *Id.* As stated previously, the specification teaches in detail how to make the claimed polypeptides, including variants thereof, and antibodies which specifically bind PRO1753. *See, e.g.,* ¶¶ [0283]-[0315]; [0256]-[0271]; [0361]-[0379]; and Examples 6-10 (¶¶ [0453]-[0499]). In addition, the specification discloses that antibodies to claimed polypeptides can be used in diagnostic assays to detect the expression of PRO1753 in specific types of tissue. *See e.g., Specification* at [0407].

Thus, there is significant guidance how to make and use the claimed polypeptides. In addition, as the disclosure and references cited in the specification make clear, the production of polypeptides, polypeptide variants, and specific antibodies is a predictable and well established aspect of the biological sciences. *See, e.g., In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) (reversing the Board's decision of non-enablement and holding that as of 1980, undue experimentation was not required to make high-affinity monoclonal antibodies to a target peptide); *Sutcliffe et al.,* Science (1983) 219:660-666 at 661-662 (teaching that "by following simple rules, one can in general select peptides that will elicit antibodies reactive with intact proteins").

In conclusion, the PTO's rejection based on lack of utility has been addressed above, and the PTO has otherwise failed to meet its burden to establish a reasonable basis to question the enablement provided for the claimed invention. Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO maintains the rejection of pending Claims 14-17 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement. *Office Action* at 17-20.

The PTO has Failed to Meet Its Initial Burden of Rebutting the Presumption that the Pending Claims are Adequately Described

To overcome the presumption that the claimed subject matter is adequately described, the PTO must present "evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 U.S.P.Q. at 97." *M.P.E.P.* § 2163.04. To support its rejection of pending Claims 14-17, the PTO has merely repeated, nearly verbatim, the same arguments made in support of its enablement rejection. For the reasons discussed above, these arguments are fundamentally flawed because the mischaracterize the claimed subject matter.

The PTO argues that:

> The specification intends immunologically active peptides to also retain biological activity of a native or naturall -occurring PRO, as indicated below:
>
> > "Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231.

> Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO: 110, and possessing any and/or all underlying biological activities. However, the does not describe any biological activity of the native or naturally-occurring PRO1753 polypeptide SEQ ID NO: 110. *Office Action* at 18 (emphasis added).

As noted previously, "[a] description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." *M.P.E.P.* § 2163.04 (emphasis added). Therefore "[t]he examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." *Id.* The above arguments fail to meet this burden because they are fundamentally flawed for at least two reasons.

First, the PTO is relying on a definition of the term "active" or "activity" found in the specification. However, the claims at issue do not use the terms "active" or "activity." Therefore, the PTO is impermissibly importing a limitation into the claims from the specification.

Second, even if the PTO were correct to suggest that the claimed polypeptides of claims 14-17 were required to be "active," nothing in the quoted portion of the specification suggests that the "specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO" as the PTO suggests. The PTO quotes the specification as stating "'biological' activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO **other than the ability to induce the production of an antibody** against an antigenic epitope possessed by a native or naturally-occurring PRO and an 'immunological' activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO." Thus, Applicants clearly contemplated that "biological" activity was distinct from "immunological" activity. In addition, according to the PTO, the specification teaches that "'Active' or 'activity' for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological **and/or** an immunological activity of native or naturally-occurring PRO." Clearly, Applicants contemplated that an "active" polypeptide can have "biological activity" **or** "immunological activity." Thus, the specification clearly teaches that a PRO polypeptide can retain "biological"

activity, which does not include immunological activity, "immunological" activity, which does not include biological activity, **or** both.

Therefore, even if Applicants have failed to disclose the "biological" activity of the PRO polypeptide as the PTO asserts, this is not relevant to the written description of the claims at issue because: (1) the claims do not recite the defined terms "active," "activity," "biological activity" or "immunological activity;" and (2) nothing in the specification requires immunologically active polypeptides to also be "biologically active."

The PTO also argues that making claimed variants is not as predictable as making nucleic acids that encode a particular amino acid sequence because "the claimed variant polypeptides are all different polypeptides ... that vary anywhere and everywhere from SEQ ID NO: 110, within the metes and bounds of the recited percent identity." *Office Action* at 19. The PTO also argues that unlike biological activity, the function of being used to generate an antibody to specifically detect the polypeptide of SEQ ID NO: 110 does not limit the claimed variants in any discernable, predictable or disclosed manner. *Id.*

These arguments do not address the teaching of the *In re Wallach* case and Example 14 of the Written Description Guidelines. The *Wallach* case states that "we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004) (emphasis added). Likewise, it is a routine matter to generate the list of polypeptides which have either 95% or 99% amino acid with SEQ ID NO:110 as disclosed in the specification. Example 14 discloses that there is sufficient written description where a percent sequence identity is recited to a disclosed sequence, and a test is disclosed to determine if the variant polypeptide posses the function of the disclosed sequence. There in nothing in Example 14 that requires that the recited function limit the structure of the variant protein in any "discernable, predictable or disclosed manner." Here, Applicants have recited the function "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:110 in esophageal tissue

samples." Based on the disclosure of the application as filed and the skill in the art, a skilled artisan can test variant polypeptides to determine if they retain this function.

Finally, the PTO also argues that:

> Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal samples is essential to Applicants' claimed genus of variant polypeptides. The specification defines antibody specificity as follows:
>
> > An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.
>
> The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. Therefore, the function of the claimed variants is not related to the structure of the claimed variants. Therefore, the skilled artisan would not recognize the disclosure of SEQ ID NO: 110 as putting Applicants in possession of the claimed genus. *Office Action* at 19-20.

Applicants maintain that Claims 14-17 do not require that the variant polypeptides of Claims 14-17 are capable of generating antibodies which bind the polypeptide of SEQ ID NO:110 without binding to the variant polypeptides themselves. Rather, the subject matter within the scope of Claims 14-17 includes variant polypeptides which can be used to generate antibodies which bind to both the variant polypeptide used to generate them and to the polypeptide of SEQ ID NO:110, but which antibodies "can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples." Indeed, the PTO will appreciate that, in view of the high degree of homology between the polypeptides of Claims 14-17 and the polypeptide of SEQ ID NO:110, there are many antibodies which will bind to both polypeptides and, accordingly, the polypeptides of Claims 14-17 are useful for producing antibodies which can be used as diagnostic agents for detecting the polypeptide of SEQ ID NO:110 in a sample.

In conclusion, because all of the PTO's arguments are fundamentally flawed, the PTO has failed to meet its "initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." *M.P.E.P.* § 2163.04. And even if it has met this burden, Applicants

submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:110, by specifying a high level of amino acid sequence identity, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Nov. 7, 2006

By: _____
AnneMarie Kaiser
Registration No. 37,649
Attorney of Record
Customer No. 30,313
(619) 235-8550

3023314
101606